No agreement was reached regarding further allowable subject matter. Applicants' attorney indicated that a response to the final rejection would be filed.

The Rejection of Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47

Under 35 U.S.C. §§ 102(b)/103(a)

Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over Davaran et al. (Davaran et al., "Hydrophilic Copolymers Prepared From Acrylic Type Derivatives of Ibuprofen Containing Hydrolyzable Thioester Bond," *European Polymer Journal 34*(2):187-192, 1998), as evidenced by the present application, Baroni et al. (Baroni et al., "Effect of Ibuprofen and Warfarin on the Allosteric Properties of Haem-Human Serum Albumin," *European Journal of Biochemistry 268*:6214-6220, 2001), Ito et al. (Ito et al., "Control of Water Permeation by pH and Ionic Strength through a Porous Membrane Having Poly(carboxylic acid) Surface-Grafted" *Macromolecules 25*:7313-7316, 1992), and U.S. Patent No. 6,358,490, issued to Theodore et al. Withdrawal of the rejection is requested for the following reasons.

The Davaran reference is directed to hydrophilic copolymers of S-methacryloyloxyethyl-α-methyl-4(2-methylpropyl)benzene thioacetate (MOETE). According to the Examiner, the Davaran reference teaches hydrophilic copolymers that include a methylacrylic acid hydrophobic component, water-soluble PEG, and an ester bond linking the PEG to the methylacrylic acid polymer backbone.

The Examiner concludes that the combined teachings of the cited references anticipate or render obvious the claimed invention. Applicants respectfully disagree.

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Claims 36, 38, 41, and 47 are the pending independent claims. Claims 3, 4, 8, 9, 13-15, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

The claimed invention, as recited in independent Claims 36, 38, 41, and 47, relates to a water-soluble hydrophilic conjugate that includes two components, a hydrophilic component and a hydrophobic component, that are linked by a pH-sensitive linkage. The pH-sensitive linkage is stable at a pH between 6.8 and 8 and is hydrolyzed at a pH less than 6.5. The hydrophobic component is endosomal membrane disruptive when released from the hydrophilic conjugate by hydrolysis of the pH-sensitive linkage. The hydrophilic component includes a polyalkylene oxide. Each of the elements noted above is recited in each of independent Claims 36, 38, 41, and 47.

Applicants submit that the independent claims' recitation that the hydrophobic component is endosomal membrane disruptive must be afforded patentable weight.

The claimed invention requires that the hydrophobic component is endosomal membrane disruptive. The recitation clearly places a requirement on the hydrophobic component of the claimed conjugate: it must be endosomal membrane disruptive. Hydrophobic components that are not endosomal membrane disruptive are not within the scope of the claimed invention, they are excluded from the scope of the claimed invention.

Because the hydrophobic component released by the hypothetical hydrolysis of the copolymer described in the Davaran reference is a poly(methacrylic acid), which has been evidenced in the record of this application's prosecution as not being disruptive to endosomal membrane (see Stayton Declaration), the Davaran reference does not describe a copolymer having a hydrophobic component that is endosomal membrane disruptive. For this reason, withdrawal of the rejection is respectfully requested.

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Furthermore, there is no apparent reason to modify Davaran's teaching to arrive at the claimed invention. The Davaran reference discloses polymeric-drug conjugates for delivering ibuprofen to solve the drug's irritant side effects on the gastro-enteric mucosa and its poor water solubility. Because the problem associated with the solubility of the polymeric prodrug has been satisfactorily solved by using the disclosed hydrophilic comonomers and further because polyethylene glycol methacrylate (PEGM) is well-known in the field of art as a solution for solubilizing hydrophobic drugs or polymers, there is no apparent reason to modify Davaran's teaching to arrive at the claimed invention.

Regarding the Stayton Declaration mentioned above, the Examiner appears to be of the opinion that the Declaration is insufficient to overcome the rejection. Specifically, the Examiner states that poly(methacrylic acid) meets the requirement on being "membrane disruptive" because the Declaration shows at least "minimal" membrane disruption results from the use of poly(methacrylic acid) and there are no "basement" values set in the claimed invention. In addition, the Examiner claims that the Declaration refers only to hemoglobin hemolysis and does not provide evidence that poly(methacrylic acid) would not disrupt other membranes. Applicants respectfully disagree.

The Examiner has taken an extreme and unreasonable view of the membrane disruption data. The claimed invention is directed to compositions and methods for delivery of therapeutic, diagnostic, or prophylactic agents for treatment or diagnostic purpose. According to the specification, "a membrane disruptive agent . . . becomes membrane disruptive following endocytosis, releasing cellular contents or releasing a therapeutic, diagnostic or prophylactic agent to be delivered" (page 6, lines 10-14). Any membrane disrupting agent disrupts the membrane or interstitial spacing such that the agent to be delivered passes through the cell or cell layer(s) (page 10, lines 9-10). The Declaration shows that poly(methacrylic acid) has a

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hemolysis activity close to zero. Such an extremely low hemolytic activity is meaningless in light of the definition of the term "endosomal membrane disruptive" according to the specification. Applicants submit that poly(methacrylic acid) is not endosomal membrane disruptive as defined by the specification.

The Office Action states that inferences can be drawn from the teachings of the cited references and that "applicants' arguments that poly(methacrylic acid) is insufficiently hydrophobic to be endosomal membrane disruptive suggests that at least it is endosomal membrane disruptive albeit not of greater effect as the higher homologs alkyl poly(alkylacrylic acids)." (Emphasis added.) Applicants respectfully disagree with the Examiner's conclusion that applicants' statement "suggests" that poly(methacrylic acid) is at least somewhat endosomal membrane disruptive. Quite to the contrary, it is clear from the record that applicants suggest no such thing. Applicants have evidenced that poly(methacrylic acid) is not endosomal membrane disruptive. Applicants have not equivocated on this point. There has been no suggestion by applicants, nor has the Examiner provided any evidence, that poly(methacrylic acid) is endosomal membrane disruptive. Absent any evidence to support the Examiner's position that poly(methacrylic acid) is endosomal membrane disruptive, withdrawal of the rejection is requested.

Further in regard to the Stayton Declaration, the Office Action states that the Declaration is drawn to three polymers and is not a showing commensurate in scope with the claims and that "unexpected results" must establish that there is a difference between the claimed invention and the cited art. The Declaration was not provided for the purpose of enabling the invention across its scope, nor was the Declaration presented to demonstrate unexpected results. The Declaration was provided to evidence the simple fact that poly(methacrylic acid) is not endosomal membrane disruptive. The Davaran reference describes a polymer arguably releasing a hydrophobic

component on hydrolysis that the Examiner has equated to being endosomal membrane disruptive. That hydrophobic component is poly(methacrylic acid). The Declaration merely evidences that poly(methacrylic acid) is not endosomal membrane disruptive and therefore establishes that the Examiner's position, that poly(methacrylic acid) is endosomal membrane disruptive, is untenable. Because the record has evidenced that poly(methacrylic acid) is not endosomal membrane disruptive and no evidence has been provided to indicate otherwise, withdrawal of the rejection is requested.

For the reasons set forth above, the Davaran reference fails to describe a copolymer that releases a hydrophobic component that is endosomal membrane disruptive. There is no motivation, suggestion, or apparent reason to combine the cited references or modify Davaran's conjugate to arrive at the claimed invention. Therefore, the claimed invention is novel and nonobvious in view of the cited references. Withdrawal of the rejection is requested.

The Rejection of Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 Under 35 U.S.C. § 103(a).

Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of the Davaran reference in view of U.S. Patent No. 4,571,400, issued to Arnold, and Vinogradov et al. (Vinogradov et al., "Self-Assembly of Polyamine-Poly(ethylene glycol) Copolymers with Phosphorthioate Oligonucleotides," *Bioconjugate Chemistry* 9(6):805-812, 199), as evidenced by the present application, the Baroni reference, the Ito reference, and the Theodore reference. Withdrawal of the rejection is requested for the following reasons.

Claims 3, 4, 8, 9, 13-17, 19, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

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The Vinogradov reference teaches cationic copolymer for DNA delivery by conjugating poly(ethylene glycol) (PEG) and polyamines: polyspermine (PSP) and polyethylenimine (PEI). The cationic copolymers include the conjugates of polyethylene glycol (PEG) and polyamines. The PEG and the polyamines are linked through a carbamate linker, i.e., -NH-COO-. The cationic copolymers are complexed to antisense oligonucleotides (PS-ODNS).

The Arnold reference is directed to pharmaceutical compositions containing dihydrocodeine or a pharmaceutically acceptable acid addition salt thereof and ibuprofen or a pharmaceutically acceptable salt thereof that are useful in treating pain. The reference discloses a wide range of pharmaceutically acceptable carriers for use with ibuprofen.

Because neither the Vinogradov reference nor the Arnold reference discloses a polymer that is endosomal membrane disruptive at endosomal pH, the deficiencies of the teachings of the Davaran, Baroni, Ito, and Theodore references noted above with regard to independent Claims 36, 38, 41, and 47 are not cured by the teachings of the Vinogradov and Arnold references.

Because the cited references fail to teach, suggest, provide any motivation, or otherwise render obvious the claimed invention, the claimed invention is not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

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CONCLUSION

In view of above amendments and foregoing remarks, applicants believe that Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are in condition for allowance. If any issue remains that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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